

Benzylpenicillin sodium 600mg and 1200mg Powder for Injection

Technical Leaflet

PRODUCT SUMMARY

Qualitative and Quantitative Composition

Benzylpenicillin sodium available as 600 mg and 1200 mg vials.

Pharmaceutical Form

White crystalline, water-soluble sterile powder for injection.

CLINICAL PARTICULARS

Therapeutic indications:

Benzylpenicillin is indicated for most wound infections, pyogenic infections of the skin, soft tissue infections and infections of the nose, throat, nasal sinuses, respiratory tract and middle ear, etc.

It is also indicated for the following infections caused by penicillin-sensitive microorganisms: Generalised infections, septicaemia and pyaemia from susceptible bacteria. Acute and chronic osteomyelitis, sub-acute bacterial endocarditis and meningitis caused by susceptible organisms. Suspected meningococcal disease. Gas gangrene, tetanus, actinomycosis, anthrax, leptospirosis, rat-bite fever, listeriosis, severe Lyme disease, and prevention of neonatal group B streptococcal infections. Complications secondary to gonorrhoea and syphilis (e.g. gonococcal arthritis or endocarditis, congenital syphilis and neurosyphilis). Diphtheria, brain abscesses and pasteurellosis.

Consideration should be given to official local guidance (e.g. national recommendations) on the appropriate use of antibacterial agents.

Susceptibility of the causative organism to the treatment should be tested (if possible), although therapy may be initiated before the results are available.

Posology and method of administration

Route of administration:

Intramuscular, intravenous.

Preparation of solutions:

Pharmaceutical preparation

Only freshly prepared solutions should be used. Reconstituted solutions of benzylpenicillin sodium are intended for immediate administration.

600 mg vial

Intramuscular injection: 600 mg (1 mega unit) is usually dissolved in 1.6 to 2 ml of Water for Injections BP.

600 mg and 1200 mg vials

Intravenous Injection: A suitable concentration is 600 mg (1 mega unit) dissolved in 4 to 10 ml of Water for Injections BP or Sodium Chloride Injection BP and 1200 mg (2 mega units) dissolved in at least 8 ml of Sodium Chloride Injection BP or Water for Injections BP.

Intravenous Infusion: It is recommended that 600 mg (1 mega unit) should be dissolved in at least 10 ml of Sodium Chloride Injection BP or Water for Injections BP and 1200 mg (2 mega units) should be dissolved in at least 20 ml of Sodium Chloride Injection BP or Water for Injections BP. Sodium overload and/or heart failure may occur if benzylpenicillin sodium is administered in sodium-containing solvents to patients who suffer from renal failure and/or heart failure. Therefore, for such patients, benzylpenicillin sodium should not be reconstituted in sodium-containing liquids such as Sodium Chloride Injection BP or Ringer's solution.

Dosage and administration:

The following dosages apply to both intramuscular and intravenous injection.

Alternate sites should be used for repeated injections.

Adults

600 to 3,600 mg (1 to 6 mega units) daily, divided into 4 to 6 doses, depending on the indication. Higher doses (up to 14.4 g/day (24 mega units) in divided doses) may be given in serious infections such as adult meningitis by the intravenous route.

In bacterial endocarditis, 7.2 to 12 g (12 to 20 mega units) or more may be given daily in divided doses by the intravenous route, often by infusion.

Doses up to 43.2 g (72 mega units) per day may be necessary for patients with rapidly spreading gas gangrene.

High doses should be administered by intravenous injection or infusion, with intravenous doses in excess of 1.2g (2 mega units) being given slowly, taking at least one minute for each 300 mg (0.5 mega unit) to avoid high levels causing irritation of the central nervous system and/or electrolyte imbalance.

High dosage of benzylpenicillin sodium may result in hypernatraemia and hypokalaemia unless the sodium content is taken into account.

For the prevention of Group B Streptococcal disease of the newborn, a 3 g (5 mega units) loading dose should be given to the mother initially, followed by 1.5 g (2.5 mega units) every 4 hours until delivery.

Children aged 1 month to 12 years

100 mg/kg/day in 4 divided doses; not exceeding 4 g/day.

Infants 1-4 weeks

75 mg/kg/day in 3 divided doses.

Newborn Infants

50 mg/kg/day in 2 divided doses.

Meningococcal disease

Children 1 month to 12 years:

180-300 mg/kg/day in 4-6 divided doses, not exceeding 12 g/day.

Infants 1-4 weeks: 150 mg/kg/day in 3 divided doses.

Newborn infants: 100 mg/kg/day in 2 divided doses.

Adults and children over 12 years:

2.4 g every 4 hours

Suspected meningococcal disease

If meningococcal disease is suspected general practitioners should give a single dose of benzylpenicillin sodium, before transferring the patient to hospital, as follows:

Adults and children over 10 years: 1,200 mg IV (or IM)

Children 1-9 years: 600 mg IV (or IM)

Children under 1 year: 300 mg IV (or IM)

Premature babies and neonates

Dosing should not be more frequent than every 8 or 12 hours in this age group, since renal clearance is reduced at this age and the mean half-life of benzylpenicillin may be as long as 3 hours. Since infants have been found to develop severe local reactions to intramuscular injections, intravenous treatment should preferably be used.

Patients with renal insufficiency

For doses of 0.6-1.2 g (1-2 mega units) the dosing interval should be no more frequent than every 8-10 hours.

For high doses e.g. 14.4 g (24 mega units) required for the treatment of serious infections such as meningitis, the dosage and dose interval of benzylpenicillin sodium should be adjusted in accordance with the following schedule:

Creatine clearance (ml per minute)	Dose (g)	Dose (mega units)	Dosing interval (hours)
125	1.2	2	2
	or 1.8	or 3	3
60	1.2	2	4
40	0.9	1.5	4
20	0.6	1.0	4
10	0.6	1.0	6
Nil	0.3	0.5	6
	or 0.6	or 1.0	8

The dose in the above table should be further reduced to 300 mg (0.5 mega units) 8 hourly if advanced liver disease is associated with severe renal failure.

If haemodialysis is required, an additional dose of 300 mg (0.5 mega units) should be given 6 hourly during the procedure.

Elderly Patients

Elimination may be delayed in elderly patients and dose reduction may be necessary.

Contraindications

Allergy to penicillins. Hypersensitivity to any ingredient of the preparation.

Cross allergy to other beta-lactams such as cephalosporins should be taken into account.

Special warnings, special precautions

600mg benzylpenicillin contains 38.7mg (1.68mmol) sodium (main component of cooking/table salt) in each dosage unit. This is equivalent to 1.93% of the recommended maximum daily dietary intake of sodium for an adult.

Benzylpenicillin sodium is also used for the prevention of infection in newborn babies (specifically group B streptococcal infection).

2. BEFORE YOU USE BENZYLPENICILLIN INJECTION

Do not use Benzylpenicillin Injection if you:

- are allergic (hypersensitive) to benzylpenicillin sodium, any other antibiotics (in particular other penicillins, cephalosporins or beta-lactams) or any of the other ingredients (see section 6 - Further information).

Take special care with Benzylpenicillin Injection if you:

- suffer from other allergies, especially an allergy to medicines
- are pregnant, breast-feeding or think you could be pregnant
- have kidney problems
- have liver problems
- have any heart problems
- are diabetic.

Using other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Take care if you are taking any of the following medicines:

- oral contraceptives
- probenecid for the treatment of gout (inflammation of the joints, especially the big toe)
- methotrexate for the treatment of certain cancers
- allopurinol or sulfapyrazone - treatments for gout
- neomycin - an antibiotic
- anti-coagulants - medicines that prevent blood clots
- oral typhoid vaccine.

1200mg benzylpenicillin contains 77.4mg (3.36 mmol) of sodium (main component of cooking/table salt) in each dosage unit. This is equivalent to 3.86% of the recommended maximum daily dietary intake of sodium for an adult. 5 dosage units of 1200mg benzylpenicillin (or 10 dosage units of 600mg benzylpenicillin) reflects the lowest number of dosage units for which the threshold of 17mmol (391mg) of sodium is reached. This should be taken into account for those on a low salt (sodium) diet.

Massive doses of benzylpenicillin sodium can cause hypokalaemia and sometimes hypernatraemia. Use of a potassium-sparing diuretic may be helpful. In patients undergoing high-dose treatment for more than 5 days, electrolyte balance, blood counts and renal functions should be monitored.

In the presence of impaired renal function, large doses of penicillin can cause cerebral irritation, convulsions and coma.

Skin sensitisation may occur in persons handling the antibiotic and care should be taken to avoid contact with the substance.

It should be recognised that any patient with a history of allergy, especially to drugs, is more likely to develop a hypersensitivity reaction to penicillin. Patients should be observed for 30 minutes after administration and if an allergic reaction occurs the drug should be withdrawn and appropriate treatment given.

Delayed absorption from the intramuscular depot may occur in diabetics.

Prolonged use of benzylpenicillin may occasionally result in an overgrowth of non-susceptible organisms or yeast and patients should be observed carefully for superinfections.

Pseudomembranous colitis should be considered in patients who develop severe and persistent diarrhoea during or after receiving benzylpenicillin. In this situation, even if *Clostridium difficile* is only suspected, administration of benzylpenicillin should be discontinued and appropriate treatment given.

Interaction with other medicaments and other forms of medication

The efficacy of oral contraceptives may be impaired under concomitant administration of benzylpenicillin sodium, which may result in unwanted pregnancy. Women taking oral contraceptives should be aware of this and should be informed about alternative methods of contraception.

There is reduced excretion of methotrexate (and therefore increased risk of methotrexate toxicity) when used with benzylpenicillin sodium.

Probenecid inhibits tubular secretion of benzylpenicillin sodium and so may be given to increase the plasma concentrations.

Penicillins may interfere with:

- Urinary glucose tests
- Coombs' tests
- Tests for urinary or serum proteins
- Tests which use bacteria e.g. Guthrie test

Pregnancy and lactation

Benzylpenicillin sodium has been taken by a large number of pregnant women and women of childbearing age without an increase in malformations or other direct or indirect harmful effects on the foetus having been observed.

Although it is not known if benzylpenicillin sodium may be excreted into the breast milk of nursing mothers, it is actively transported from the blood to milk in animals and trace amounts of other penicillins in human milk have been detected.

Probenecid may make the effects of Benzylpenicillin last for longer. Benzylpenicillin can make it more likely to get side-effects from methotrexate and can sometimes make oral contraceptives less effective, resulting in unplanned pregnancy. Penicillins can interfere with the results of certain urine and blood tests.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Sodium Content

600mg benzylpenicillin contains 38.7mg (1.68mmol) sodium (main component of cooking/table salt) in each dosage unit. This is equivalent to 1.93% of the recommended maximum daily dietary intake of sodium for an adult. 1200mg benzylpenicillin contains 77.4mg (3.36 mmol) of sodium (main component of cooking/table salt) in each dosage unit. This is equivalent to 3.86% of the recommended maximum daily dietary intake of sodium for an adult. Talk to your doctor or pharmacist if you need 5 or more dosage units of 1200mg benzylpenicillin (or 10 or more dosage units of 600mg benzylpenicillin) for a prolonged period, especially if you have been advised to follow a low salt (sodium) diet.

3. HOW TO USE BENZYLPENICILLIN INJECTION

Your doctor will mix the benzylpenicillin sodium powder with an injection solution, which is usually water for injections or sodium chloride, before injecting it. (Sodium chloride injection will not be used if you have kidney or heart problems.)

Your medicine will be injected either intramuscularly (into the muscle) or intravenously (into a vein). Repeated injections will be given at different sites. Infants and diabetics will normally receive Benzylpenicillin into a vein.

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Please read the back of this leaflet.



PACKAGE LEAFLET: INFORMATION FOR THE USER

Benzylpenicillin sodium 600mg and 1200mg Powder for Injection

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side-effects get serious, or if you notice any side-effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

- What Benzylpenicillin Injection is and what it is used for
- Before you use Benzylpenicillin Injection
- How to use Benzylpenicillin Injection
- Possible side-effects
- How to store Benzylpenicillin Injection
- Further information

1. WHAT BENZYLPENICILLIN INJECTION IS AND WHAT IT IS USED FOR

Benzylpenicillin sodium 600mg and 1200mg Powder for Injection is referred to as "Benzylpenicillin Injection" in this leaflet. It contains benzylpenicillin sodium, also known as penicillin G. Benzylpenicillin sodium is one of a group of medicines known as penicillins, which are antibiotics. Antibiotics are used to kill the bacteria (germs) which cause infections.

Benzylpenicillin sodium is used to treat infections of the:

- ear
- nose
- throat
- chest
- heart
- bones
- skin.

It may also be used to treat:

- some sexually transmitted infections (gonorrhoea and syphilis)
- meningitis
- brain abscesses
- gangrene (decay and death of tissue due to lack of blood supply)
- blood infections
- anthrax (an infection from animals)
- tetanus
- diphtheria (acute infections/disease of the respiratory tract)
- listeria (a type of food poisoning)
- leptospirosis (an infection from animals)
- pasteurellosis (an infection following animal bites)
- severe Lyme disease (an infection from tick bites)
- actinomycosis (an infection caused by trauma/surgery)
- some infections caused by rat bites.



Technical Leaflet (continued)

Effects on ability to drive and use machines

None

Undesirable effects

Blood and Lymphatic System Disorders

Rare (0.01% - 0.1%)

Haemolytic anaemia and granulocytopenia (neutropenia), agranulocytosis, leucopenia and thrombocytopenia, have been reported in patients receiving prolonged high doses of benzylpenicillin sodium (eg. Subacute bacterial endocarditis).

Immune System Disorders

Very Common (>10%)

Patients undergoing treatment for syphilis or neurosyphilis with benzylpenicillin may develop a Jarisch-Herxheimer reaction.

Common (1-10%)

Hypersensitivity to penicillin in the form of rashes (all types), fever, and serum sickness may occur (1-10% treated patients). These may be treated with antihistamine drugs.

Rare (0.01%-0.1%)

More rarely, anaphylactic reactions have been reported (<0.05% treated patients).

Nervous System Disorders

Rare (0.01%-0.1%)

Central nervous system toxicity, including convulsions, has been reported with massive doses over 60 g per day and in patients with severe renal impairment.

Renal and Urinary Disorders

Rare (0.01%-0.1%)

Interstitial nephritis has been reported after intravenous benzylpenicillin sodium at doses of more than 12 g per day.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

Overdose

Excessive blood levels of benzylpenicillin sodium can be corrected by haemodialysis.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Beta-lactamase sensitive penicillins. ATC code: J01 CE01.

General Properties:

benzylpenicillin sodium is a beta-lactam antibiotic. It is bacteriocidal by inhibiting bacterial cell wall biosynthesis.

Breakpoints:

The tentative breakpoints (British Society for Antimicrobial Chemotherapy, BSAC) for benzylpenicillin sodium are as follows:

Organism	S ≤(mg/L)	I (mg/L)	R ≥ (mg/L)
Streptococcus pneumoniae Neisseria gonorrhoeae	0.06	0.12–1.0	2.0
Neisseria meningitidis	0.06		0.12
Haemolytic streptococci Staphylococci Moraxella catarrhalis Haemophilus influenzae	0.12		0.25
Rapidly growing anaerobes	1.0		2.0

S = Susceptible, I = Intermediate susceptibility, R = Resistant

Susceptibility:

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. The following table gives only approximate guidance on **probabilities** whether micro organisms will be susceptible to benzylpenicillin sodium or not.

Susceptible and intermediately susceptible micro-organisms		
Type of Micro-organism	Micro-organism	Range of required resistance
Aerobic Gram-positive micro-organisms	• Bacillus anthracis	0%**
	• Corynebacterium diphtheriae	0%*
	• Haemolytic streptococci (including Streptococcus pyogenes)	0%*-3%**
	• Listeria monocytogenes	0%**
	• Streptococcus pneumoniae • Streptococcus viridans	4%*-40%** 3-32%*
Aerobic Gram-negative micro-organisms	• Neisseria gonorrhoeae	9-10%*
	• Neisseria meningitidis	18%*
	• Pasteurella multocida	0%***
Anaerobic micro-organisms	• Actinomyces israelii	8%**
	• Fusobacterium nucleatum and Fusobacterium necrophorum	Usually sensitive
	• Gram-positive sporing bacilli (including Clostridium tetani and Clostridium perfringens (welchii))	14%**
	• Gram-positive cocci (including peptostreptococcus)	7%*
Other micro-organisms	• Borrelia burgdorferi	Usually sensitive
	• Capnocytophaga canimorsus	Usually sensitive
	• Leptospirae	Usually sensitive
	• Streptobacillus moniliformis and spirillum minus	Usually sensitive
	• Treponema pallidum	0%***

* UK data, ** European data, ***Global data

Insusceptible micro-organisms		
Type of Micro-organism	Micro-organism	Range of acquired resistance
Aerobic Gram-positive micro-organisms	• Coagulase negative Staphylococcus	71-81%*
	• Enterococcus Spp	Resistant
	• Staphylococcus aureus	79-87%*
Aerobic Gram-negative micro-organisms	• Acinetobacter	Resistant
	• Bordetella pertussis	Generally resistant
	• Brucella spp.	Resistant
	• Enterobacteriaceae (including Escherichia coli, Salmonella, Shigella, Enterobacter, Klebsiella, Proteus, Citrobacter).	Generally resistant
	• Haemophilus influenzae • Pseudomonas	Resistant Resistant
Anaerobic micro-organisms	• Bacteroides fragilis	100%***

* UK data, ** European data, ***Global data

Other Information:

Known Resistance Mechanisms and Cross-resistance

Penicillin resistance can be mediated by alteration of penicillin binding proteins or development of beta-lactamases.

Resistance to penicillin may be associated with cross-resistance to a variety of other beta lactam antibiotics either due to a shared target site that is altered, or due to a beta-lactamase with a broad range of substrate molecules. In addition to this, cross resistance to unrelated antibiotics can develop due to more than one resistance gene being present on a mobile section of DNA (e.g. plasmid, transposon etc) resulting in two or more resistance mechanisms being transferred to a new organism at the same time.

Pharmacokinetic properties

Benzylpenicillin sodium rapidly appears in the blood following intramuscular injection of water-soluble salts and maximum concentrations are usually reached in 15-30 minutes. Peak plasma concentrations of about 12 mcg/ml have been reported after doses of 600 mg with therapeutic plasma concentrations for most susceptible organisms detectable for about 5 hours. Approximately 60% of the dose injected is reversibly bound to plasma protein.

In adults with normal renal function the plasma half-life is about 30 minutes. Most of the dose (60-90%) undergoes renal elimination, 10% by glomerular filtration and 90% by tubular secretion. Tubular secretion is inhibited by probenecid, which is sometimes given to increase plasma penicillin concentrations. Biliary elimination of benzylpenicillin sodium accounts for only a minor fraction of the dose.

Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SmPC.

- reduction in blood cell count and anaemias which might make you feel tired or dizzy
- low levels of potassium in the blood
- high levels of sodium in the blood
- inflammation of the kidney
- skin irritation, fever, headache, sore throat, sore muscles and fast heartbeat particularly in patients being treated for syphilis (a sexually transmitted disease)
- diarrhoea, which may, rarely, have blood in it
- thrush or infections with other germs
- fits (convulsions).

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE BENZYLPENICILLIN INJECTION

Keep out of the sight and reach of children.

Benzylpenicillin Injection vials should be stored below 25°C. Once the content of the vial has been mixed with an injection solution, it should be used immediately.

They should not use a bottle after the expiry date printed on the bottle label. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

PHARMACEUTICAL PARTICULARS

List of excipients

None

Incompatibilities

benzylpenicillin sodium and solutions that contain metal ions should be administered separately.

Benzylpenicillin sodium should not be administered in the same syringe/giving set as amphotericin B, cimetidine, cytarabine, flucloxacillin, hydroxyzine, methylprednisolone, or promethazine since it is incompatible with these drugs.

Shelf-life

Unopened 36 months.

Reconstituted product should be used immediately.

Special precautions for storage

Store below 25°C.

Nature and contents of container

Tubular type III glass vials sealed with bromobutyl rubber plugs with aluminium overseals or plastic 'flip-top' caps. This product is supplied in vials containing 600 mg and 1.2 g of powder in boxes containing 25 vials and "GP pack" containing 2 vials of 600 mg.

Instructions for use/handling

After contact with skin, wash immediately with water. In case of contact with eyes, rinse immediately with plenty of water and seek medical advice if discomfort persists.

MARKETING AUTHORISATION HOLDER

Genus Pharmaceuticals,
Linthwaite, Huddersfield, HD7 5QH, UK.

MARKETING AUTHORISATION NUMBERS

PL 06831/0213
PL 06831/0284

DATE OF FIRST AUTHORISATION/ RENEWAL OF AUTHORISATION

3 July 2008

DATE OF (PARTIAL) REVISION OF THE TEXT

November 2020



Adults

The usual dose is 600mg to 3,600mg daily. For severe infections such as meningitis and gangrene, higher daily doses of up to 14,400mg and 43,200mg respectively may be used.

Suspected Meningitis:

Benzylpenicillin is sometimes given as a single dose in cases of suspected meningitis. The usual dose is 1,200mg for adults and children over 10 years.

Meningitis:

The usual dose is 2,400mg every four hours for adults.

Prevention of infection during labour:

If Benzylpenicillin is administered during labour for the prevention of infection (specifically group B streptococcal infection) in newborn babies, 3,000mg of Benzylpenicillin should be given to the mother followed by 1,500mg every four hours until the baby is delivered.

Adults with kidney problems

Your doctor will carry out some tests to check this. You may then be given a lower dose of Benzylpenicillin Injection. Lower doses may also be given to some elderly patients.

Children

The dose for babies and children is based on their weight. The usual dose for newborn babies is 50mg per kg body weight per day and for infants (1 to 4 weeks old) is 75mg per kg body weight per day. The usual dose for children is 100mg per kg body weight per day although higher doses of up to 4,000mg per day may be given.

The daily dose may be divided into between two and six separate injections. Higher doses for severe infections are usually given by slow intravenous infusion (drip).

Meningitis:

The usual dose is 180-300mg per kg per day (up to 12g per day) for children up to 12 years old, 150mg per kg per day for infants (1 to 4 weeks old) and 100mg per kg per day for newborn babies.

Premature babies and neonates

Lower doses may also be given to these groups.

If you take more Benzylpenicillin Injection than you should

Irritation of the brain and shaking fits (convulsion) have been seen in patients when very high doses of Benzylpenicillin Injection have been given by mistake, in particular to patients with poor kidney function.

4. POSSIBLE SIDE-EFFECTS

Like all medicines, Benzylpenicillin Injection can cause side-effects, although not everybody gets them.

Tell your doctor immediately if you get any of the following side-effects:

- skin rash or itchy skin
- difficulty in breathing or tightness of the chest
- puffiness of the eyelids, face or lips
- swelling or redness of the tongue
- fever
- joint pains
- swollen lymph nodes.

The following side-effects have also been reported after either long-term use or with high doses of your medicine:

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